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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,734	06/25/2001	Bruce Joseph Roser	GJE-6089D1	2528

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EXAMINER	
PRATS, FRANCISCO CHANDLER	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/888,734	ROSER, BRUCE JOSEPH	
	Examiner	Art Unit	
	Francisco C. Prats	1651	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 December 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☒ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *14-16 and 20-22*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Francisco C. Prats
Primary Examiner
Art Unit: 1651

ATTACHMENT TO ADVISORY ACTION

The response filed December 6, 2004, has been received and considered. The Declarations of Edward G.D. Tuddenham and Sam L. Helgerson under 37 CFR 1.132 have been received and considered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

All of applicant's argument has been fully considered but is not persuasive of error. While applicant urges that the combination of Curtis and Livesey is legally deficient, this conclusion ignores the plain disclosure of the references. One of ordinary skill clearly would have derived from the disclosure of the references that the claimed preservative agent, trehalose, was well known to be suitable for preserving the claimed therapeutic agent, Factor VIII, in the absence of albumin, using the claimed steps. Thus, the references have the use of trehalose in the preservation of Factor VIII as the common disclosure, and therefore meet the *Rouffet* commonality element urged by applicant as being missing. Moreover, by urging that a specific format is required in obviousness determinations, applicant ignores the actual wording of § 103(a), which simply states that one may not obtain a patent "if the differences between the subject matter sought to be patented

and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

The only difference between the claims and the prior art here is that Livesey does not provide a single embodiment wherein trehalose is used to preserve native Factor VIII, and Curtis uses activated Factor VIII, rather than native Factor VIII. However, both references suggest that the claimed agent, trehalose, in the absence of albumin, is a cryoprotective agent useful in protecting proteins, such as Factor VIII, from damage during freeze-drying. Thus, applying § 103(a) to the facts of this case, a holding of obviousness is required. Applicant's suggestion of some sort of formulaic "combination" requirement ignores the fact that the same agent is disclosed in two prior art references as being suited to preserve Factor VIII, and therefore must be considered obvious.

To the extent that applicant urges that preservation of the two supposedly very different forms of Factor VIII (as taught by the Vehar reference) teaches away from the claimed invention, as supported by the Declarations of Edward G.D. Tuddenham and Sam L. Helgerson under Rule 132, the exact opposite is true. The fact that trehalose can be used to preserve both native and

activated factor VIII demonstrates that trehalose is recognized by the art as being a cryoprotectant suitable in a number of varied applications. The cited prior art clearly recognizes that the claimed agent, trehalose, is an established cryoprotection agent, which can be used to preserve proteins such as Factor VIII, as well as intact cells and other biological materials, when those materials are saved by freeze-drying for future use. See the entire disclosure of Livesey. The art-recognized broad applicability of trehalose in cryopreservation methods bolsters rather than undermines the holding of *prima facie* obviousness.

The argument regarding the alleged difference between a "solution," as the term is used in the claims, and "suspension," as the term appears in Livesey, similarly ignores what the prior art teaches, as well as ignoring the extrinsic evidence introduced by applicant. The definitions of the terms "solution" and "suspension" in the *College Chemistry* textbook and *Stedman's Medical Dictionary*, presented by applicant, are noted. However, applicant's reliance on these exhibits is confusing, since the definition of "solution" on page 1633 of *Stedman's Medical Dictionary* clearly states: "SEE, dispersion, ***suspension***." (Emphasis added.) Thus, while applicant urges that the art considers these terms to be different, and even

mutually exclusive, applicant's own exhibit demonstrates that the two terms at least overlap. It is therefore confusing how applicant can be "surprised" (response of December 6, 2004, page 5) that during examination the terms are being construed as encompassing common subject matter, since applicant's own exhibit explicitly states that the definition of "solution" encompasses the definition of "suspension."

Moreover, contrary to applicant's argument, and regardless of the definitions of "suspension" and "solution," one of ordinary skill practicing Livesey's invention clearly would have considered it obvious to combine native Factor VIII with a ***solution*** of trehalose-containing cryopreservative buffer, and freeze-drying the ***solution***, as taught by Livesey. Specifically, claim 1 of Livesey recites the steps of (emphasis added):

> (a) preparing a cryo***solution*** of a suspension of biological material;
> (b) nebulizing said cryo***solution*** . . . to form microdroplets; . . .
> (e) drying the cooled cryo***solution*** to form a dried cryo***solution***.

Claim 11 of Livesey goes on to recite that the drying step of claim 1 "comprises freeze drying", which is of course the same drying method recited in applicant's claims. Claim 17 goes on to recite that the biological material of claim 1 is Factor VIII, which is of course the same biological material as applicant's. The "microdroplets" of step (b) of Livesey clearly

encompass the "aliquots" recited in applicant's claims as being freeze-dried. Thus, contrary to applicant's argument, Livesey's disclosure is clearly not limited to freeze-drying "suspensions," but rather clearly discloses the freeze-drying of an aliquot of an aqueous solution of Factor VIII, exactly as recited in applicant's claims.

With respect to Curtis' alleged failure to exemplify freeze-drying as a storage option, applicant's attention is respectfully directed to column 5, lines 29-43 which read as follows:

> At a number of points in the process, protein stabilizers can be added to the Factor VIII and its activated form to further reduce or eliminate the formation of degradation products from the desired activated Factor VIII product. Examples of stabilizers include albumin, sucrose, maltose, glycine, and trehalose. If protein stabilizers are used in the compositions, the specific activity of the compositions is calculated by determining the total protein content less the amount of added protein stabilizer if any remains in the composition. Following the preparation and stabilization of the activated Factor VIII, the protein can be lyophilized and stored at reduced temperatures until the protein is to be administered, at which time it can be redissolved in sterile solution for administration.

Thus, regardless of what is exemplified, Curtis clearly contemplates lyophilizing, i.e. freeze-drying, a trehalose-containing Factor VIII composition in the absence of albumin. Applicant's statements to the contrary are simply inaccurate. While it is noted that Curtis differs from applicant's claims in using activated rather than native Factor VIII, Livesey suggests that native Factor

VIII can be stabilized in the same fashion as Curtis' activated Factor VIII. Moreover, as discussed above, the fact that trehalose can be used for both types of Factor VIII underscores the prior art recognition of trehalose as a cryoprotectant suggested in the freeze-drying of virtually any biological material, including native Factor VIII.

The lack of support for the alleged difference between the "suspension" of Livesey and the "solution" of the claims has been addressed above, as has Livesey's disclosure of the suitability of freeze-drying an aliquot of an aqueous solution of Factor VIII, exactly as recited in applicant's claims. With respect to the alleged "teaching away" by Livesey, note specifically that one cannot ignore a direct disclosure of suitable cryoprotectant embodiments having trehalose but no albumin, simply because one suitable cryoprotectant comprises both. That is, contrary to applicant's argument, the artisan of ordinary skill would not have ignored specifically claimed trehalose-containing, albumin-free, cryoprotection buffers such as those recited in the claims, for example claim 9, solution (2), simply because others were disclosed. Thus, while applicant urges that the obviousness rejections of record arbitrarily combine certain portions of the references

applicable to the claims, and improperly ignores relevant portions of the disclosure which teach away from the claims, citing *W.L. Gore*, on the current record it is clearly applicant who seeks to ignore the plain disclosure of the Livesey reference in favor of embodiments which might teach away.

Lastly, with respect to the difference between Example 5 of Livesey and the claimed subject matter, applicant makes certain assertions regarding the nature of the viral sample, i.e. whether the sample is a suspension or solution and whether the sample is freeze-dried, which lack any evidentiary and factual support on the record. The sample is brought to below freezing, and simultaneously dried. This appears to be freeze-drying. In any case, it is irrefutable that Example 5 of Livesey demonstrates that trehalose in the absence of albumin is a suitable cryoprotectant for protein-containing samples. Native Factor VIII is a protein. Native Factor VIII is a protein specifically claimed by Livesey to be amenable to the methods disclosed therein. In view of Livesey, particularly when further taken in view of the related disclosure of Curtis, one of ordinary skill clearly would have reasonably expected native Factor VIII to have been amenable to the freeze-drying techniques taught by Livesey, wherein trehalose-containing albumin-free buffers are used as cryoprotectant solutions.

In sum, applicant seeks to ignore those portions of the cited references which strongly suggest practicing the claimed invention, while viewing only those portions suggesting non-obviousness. One of ordinary skill viewing the cited references clearly would view allowance of the present claims over those references as being erroneous. Because the cited references suggest practicing the claimed invention, the holding of obviousness will be maintained.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C. Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Francisco C. Prats
Primary Examiner
Art Unit 1651

FCP